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EXAMINER: BAKALYAR, H

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/16/97; 10/4/97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-84 is/are pending in the application.
Of the above, claim(s) 3, 9, 11, 17-21, 23-27, 39-84 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-2, 4-10, 12-16, 22, 28-38 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☒ Some* ☐ None of the CERTIFIED copies of the priority documents have been
no translation
☒ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's election with traverse of Group I, species III in Paper Nos. 15 and 12 is acknowledged. The traversal is on the ground(s) that allegedly under PCT Article 17(3)(a) the Restriction Requirement is improper. This is not found persuasive because, as Applicant is aware, the restriction requirement was made under PCT Rules 13.1 and 13.2, and Applicant has not addressed this basis for the restriction requirement. In regard to the election of species, Applicant alleges that PCT Rule 13.1 does not allow for election of species, however, inspection of Paper No. 10, page 6, reveals the election of species was made under PCT Rule 13.2. As above, Applicant has not addressed the basis under which the species requirement was made.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-2, 4-10, 12-16, 22 and 28-38 are examined.

Claim Rejections - 35 U.S.C. § 112

3. Claims 1-2, 4-10, 12-16, 22 and 28-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods for identifying one or more molecules via FCS. However, the state of the art does not allow for identification, as opposed to the detection, of a chemical species by the parameters recited in the instant claims (e.g. rotational diffusion coefficients, etc.). It is unclear how such parameters will lead to the identity of a specific

chemical entity, because though such parameters reveal information regarding, for example, size of a molecule, they in no way provide sufficient information to identify the exact chemical constitution of a molecule. One of skill in the art would not predict that identification of molecules would be possible because it is expected that a variety of chemically divergent species will have, for example, similar size and rotational diffusion coefficients. The specification provides insufficient guidance and working examples to remedy the unpredictability associated with identification of a molecule via FCS.

Therefore, in view of the discussion above, one of skill in the art would need to undertake an undue amount of experimentation to practice the invention as claimed.

4. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a method of FCS wherein the coordinates of the measuring compartment itself changes with time and defines a diffusion time of a luminescent complex.

However, one of skill in the art would not predict that motion of a compartment will correlate to diffusion of a complex contained therein, because the state of the art suggests that motion of a container should not effects its contents' innate properties. Further, the coordinates of the measuring compartment changing with time also reads on the shape of the compartment changing, and again, one of skill in the art would not predict that shape of a container will correlate to diffusion of a complex contained therein. The specification provides insufficient

guidance and working examples to remedy the unpredictability associated with the claimed correlations.

Therefore, in view of the discussion above, one of skill in the art would need to undertake an undue amount of experimentation to practice the invention as claimed.

5. Claims 1-2, 4-10, 12-16, 22 and 28-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitations of "preferably", "in particular", "especially" throughout the claims render the claims vague and indefinite. These terms do not limit the claims because they convey optional limitations, and therefore their use is confusing.

b. The recitations of "and/or" throughout the claims render the claims vague and indefinite because it is not clear what Applicant intends to be encompassed by the claims. Proper Markush language should recite either "selected from the group consisting of A, B and C" or "selected from A, B or C".

c. The terms "small", "short", "smaller", "shorten", "increased", "enhanced", "excess", "reduce", "change" recited throughout the claims are relative terms which render the claim indefinite. The terms are not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

d. The recitation of "identifying" in claim 1 is vague and indefinite because it is unclear what processes (e.g. detection, ascertainment of chemical composition or structure, or other) is encompassed by the term.

e. Claim 4 is dependent upon claim 3, which is non-elected in this application. The examiner regrets the error.

f. The claims are replete with antecedent basis problems in regard to both terminology and concept. These errors are too numerous to identify. However, a non-exhaustive list is presented below. Applicant is required to supply antecedent basis for terms and concepts throughout the claims.

For example, the following lack antecedent basis in claim 1 or intervening claims: "the measurement" line 4-5 of claim 1; "coordinates of the measuring compartment" in claim 4; "substituent" and "molecule to be determined" in claim 5; "functional evaluation" in claim 6; "measured molecules" or "molecular complexes" in claim 7; "molecular complexes", "ionic molecules", "measuring element" and "sample volume" in claim 9; "target molecule" in claim 10; "complexes", dye-labeled ligands" in claim 12; "luminophorous ligand" and "luminophorous complex" in claim 13; "measuring compartments" in claim 14; "chromatographic unit" in claim 22; "sensitivity for complex formation with dye labeled ligand" in claim 28; "detecting reaction" in claim 30; "analytes" "sample", "assay", "reaction" in claim 31; "analyte" in claim 32; "samples" in claim 33; "products" in claim 34; "oligomer or polymer distributions" and "half widths"in claim

35; "sample volume", "immobilized structure", fixed cells", "complex formation", " receptor", "involvement of solid phase", "sheets", "fluorescence depolarization", "kit" in claims 36-38.

g. The recitations of "characterized" throughout the claims are vague and indefinite because the meaning of the term is not clear. For example, does the use of "characterized" followed by method or correlations or other necessitate method steps? If so, such steps need be clearly delineated to convey to one skilled in the art what is encompassed by the claims.

h. Claims 1-2, 4-10, 12-16, 22 and 28-38 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2173.05(l). The omitted steps are: there are no clear method steps in base claim 1. To paraphrase the method of claim 1: a measurement is performed by determining parameters determined by luminescence. The claim does not recite step(s) of detection of luminescence or measurement of parameters. Further, no correlation steps are recited (e.g. it is not clear how the identity or detection of a molecule relates to luminescence, material-specific parameters or measurement of any kind) If Applicant intends dependent claims to limit to more specific methodologies, Applicant is advised the specific methodologies must be clearly claimed by use of method steps.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 5-8, 10, 15, 28-30, 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993.

Thompson et al, or Sorscher et al, or Kask et al or, Rigler et al or, Meyer et al, each teach methods for identifying (detecting) molecules in dilute solutions (dilute, therefore reads on a small number of molecules) using laser-excited FCS with measuring times of less than 500 ms (e.g. channel time 0.1 ms) in a small volume element (e.g. 10^{-15} liter and below) and short diffusion times by determining the molecules' material-specific parameters (e.g. rotational motion, rotational diffusion, translational diffusion, chemical kinetics, excitation/emission wavelengths, or lifetime of the excited state), which parameters are in turn determined by luminescence

measurements of the molecules. Rigler et al, for example, disclose that it is standard in FCS methodology to correlate translational diffusion (G(t)) with the absolute number of particles (N) and exemplify this technique with a receptor bound to a rhodamine-labeled inhibitor (reads on ligand or ligand complex, complex of ionic or non-ionic nature, and ternary complex (instant claim 30)). The general technique of FCS comprises taking fluorescent measurements in an electric or magnetic field (e.g page 104, "Theory", line 3 of Thompson), further in regard to instant claim 8 it is noted that due to Earth's natural magnetic field, a magnetic field is superimposed upon every Earthly object, including objects associated with FCS measurements.

It is further noted that terms "especially" and "preferably" recited in instant claim 1 (or elsewhere throughout the claims) do not limit the instant invention, that the use of "if" in claim 10 does not limit the invention of claim 1 to comprise an electric molecular trap and that claim 15 does not limit to more than one sample volume. The recitation of "use of kit systems" (instant claim 38) for fluorescence polarization lends no patentable weight to the invention because "kit" does not modify the reagents used in the claimed method.

9. Claims 1-2, 5-8, 9-10, 13-16, 22, 28-30, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993.

Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993, are discussed, supra.

It may be determined that the labels of the prior art references are not "luminophorous", or in particular that the labels of the prior art references do not have the particular extinction coefficient or quantum yield recited in instant claim 13. It may also be determined that configuration of measuring compartments and emergence objective are not as per instant claim 14.

If it is determined that, for example, a rhodamine label does not read on a luminophorous label, such luminophorous labels were well known in the art at the time of invention and were recognized functional equivalents with rhodamine labels, especially in FCS methodology. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute luminophorous labels for the labels of Thompson et al, or; Sorscher et al or; Kask et al, or; Rigler et al or; Meyer et al, because luminophorous labels were well known in the art at the time of invention and were recognized functional equivalents with rhodamine labels, and one of ordinary skill in the art would have been motivated to substitute with the expectation of successfully performing FCS with a functionally equivalent label.

In regard to extinction coefficient or quantum yield, the art is replete with luminous labels and it is noted that Applicant has not pointed to the criticality of these variables. Therefore, the

extinction coefficient or quantum yield in the labels used in the method are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results.

The prior art references are silent in regard to configuration of measuring compartments and emergence objective. However, it is again noted that Applicant has not pointed to the criticality of these variables. Therefore, the configuration used in the method are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results.

The prior art references are also silent in regard to use of a microdispensing system for dispensing the sample volumes. However, one of ordinary skill in the art would expect that microdispensing systems (which read on a pipetteman) would be used as the volumes are small. Alternatively, it would be obvious to one of ordinary skill in the art to dispense the sample volumes with a microdispensing system because the volumes are small.

10. Claims 1-2, 5-8, 9-10, 12-16, 22, 28-30, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993; in view of facts well known in the art.

Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993, as applied to claims 1-2, 5-8, 9-10, 13-16, 22, 28-30, 38 under U.S.C. 103 or claims 1-2, 5-8, 10, 15, 28-30, 38 under U.S.C. 102 is discussed, supra.

It may be determined that the teachings of the prior art differ from the instant invention in that the reagents are not concentrated, either by increasing the effective association rate, and the teachings of the prior art differ from the instant invention in that the reagents are not concentrated by concentrating the reactants prior to mixing them via a technique such as electrophoresis and transporting the reagents to the measuring volume element via electrophoresis.

However, it is well known that rate of chemical reactions and equilibrium concentrations of product are increased by concentration of the reacting components. All of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes. It is also well known in the art that electrophoresis may be used for concentration and /or transport of reagents and that concentration of the reacting components can be effected by reducing the effective reaction volume by changing the hydration sheath around the reactants (e.g. by adding polymers or dextrans).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to concentrate the reagents by increasing the effective association

rate of the reagents by one of the many methods known in the art (e.g. by adding polymers or dextrans) or by electrophoresis prior to mixing (reagents may be transported by electrophoresis as well) because molecular processes and equilibrium dynamics are effected by concentration of reagent and all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes. One of ordinary skill in the art would have been motivated to concentrate the reagents by increasing the effective association rate of the reagents by one of the many methods known in the art (e.g. by adding polymers or dextrans) or by electrophoresis prior to mixing because of the expectation of successfully increasing the ability of FCS to measure equilibrium dynamics or molecular processes by increasing the probability that the intermolecular processes will occur in the small test volume.

11. Claims 1-2, 5-8, 9-10, 13-16, 22, 28-30, 31-37, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages 13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993; in view of facts well known in the art.

Thompson et al Biophys. J. July 1983 volume 43 pages 103-114, or; Sorscher et al Biochimica et Biophysica Acta 610(1980) pages 28-46; Kask et al Eur Biophys J (1985) 12: 163-166, or; Rigler et al Fluorescence Spectroscopy (Wolfbeis, editor) Springer Verlag (1992) pages

13-24, or; Meyer et al, Biophys. J. (1988) volume 54 pages 983-993, as applied to claims 1-2, 5-8, 9-10, 13-16, 22, 28-30, 38 under U.S.C. 103 or claims 1-2, 5-8, 10, 15, 28-30, 38 under U.S.C. 102 is discussed, supra.

The teachings of the prior art differ from the instant invention in that (a) two analytes are not measured each with a different dye label via energy transfer or through the differing wavelengths of excitation or emission of the labels (b) in particular using the method for measurement of lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions (c) the biological materials are not presented in sheets or immobilized structure.

However, (a) energy transfer by two dyes is well known in the art to measure bimolecular or higher reaction parameters (such as distance between the reactants, etc) and all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes; (b) all of the above cited references teach that FCS may be generally applied to biological reactions and models, which will include measurement of lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions (see in particular Meyer et al for lipid); (c) it is well known that many biological systems rely on strict spatial order between components for function, and in particular Thompson et al teach an application of FCS is to study specific binding characteristics between chemical species, one of which is immobilized upon a surface (e.g. page 104, right column) and that cell integrity is important in some applications (e.g. page 104, left column, study of motion of muscle crossbridges).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to (a) use two dyes to measure two reactants in a bimolecular reaction or higher, or (b) use the method of the cited references to study lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions, or (c) immobilize the biological material on a "sheet" structure, because all of the above cited references teach either the potential or utilization of FCS to examine equilibrium dynamics or molecular processes (which can be bimolecular or higher) and (a) energy transfer by two dyes is well known in the art to measure bimolecular or higher reaction parameters (b) important biological systems amenable for FCS study including lipid-bearing vesicles or proteins made by in vitro synthesis or polymer are known, and (c) it is well known that many biological systems rely on strict spatial order between components for function and this order can be preserved by immobilizing biological structures on sheets. One of ordinary skill in the art would have been motivated to (a) use two dyes to measure two reactants in a biomolecular reaction or higher, or (b) use the method of the cited references to study lipid-bearing vesicles or proteins made by in vitro synthesis or polymer distributions, or (c) immobilize the biological material on a "sheet" structure, because of the expectation of successfully using FCS to examine important biological reactions.

Conclusion

12. Any inquiry concerning this communication should be directed to Heather Bakalyar at telephone number (703)305-7143.

The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached on (703) 308-4310. The official fax phone number for this Group is (703)308-4242.

13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group 1800 receptionist whose telephone number is (703)308-0196.

Heather Bakalyar, Ph.D.

12/22/97

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800